IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

13th Edition

Cerivastatin (Lipobay) & Gemfibrozil (Lopid)

Rhabdomyolysis is a rare, potentially life-threatening adverse reaction associated with the use of HMG-CoA reductase inhibitors (including cerivastatin) and fibrates (including gemfibrozil). Recently, post-marketing spontaneous reports of suspected ADRs have highlighted an increased incidence of rhabdomyolysis in patients receiving cerivastatin and gemfibrozil concomitantly. While such use appears to be relatively rare, the product information was recently amended to contraindicate such use and update the current warnings regarding the occurrence of rhabdomyolysis. A "Dear Healthcare Professional" letter was circulated to notify this important new safety information.

Despite these actions, reports of myopathy/rhabdomyolysis associated with concomitant use of cerivastatin and gemfibrozil continued to be reported to the company (Bayer), who voluntarily suspended marketing of cerivastatin pending further evaluation.

The EU's Pharmacovigilance Working Party is currently reviewing the issue of rhabdomyolysis associated with other HMG-CoA reductase inhibitors and any further regulatory changes considered necessary will be notified when this review has been completed.

Propofol (Diprivan/Propofol/Propofol-Lipuro)

Propofol is a short-acting intravenous anaesthetic agent, approved for sedation of ventilated adult patients in intensive care, as well as induction of general anaesthesia.

A randomised, controlled clinical trial to evaluate the safety and efficacy of propofol versus standard selective agents in paediatric ICU patients was recently carried out in the US. The results of the study showed an increase in the number of deaths in patients treated with propofol as compared to those treated with standard selective agents. The deaths failed to reveal a correlation with underlying disease status nor did they reveal a definite pattern to the causes of death.

In order to more fully understand this potential safety issue, AstraZeneca will initiate a new clinical trial designed specifically to evaluate any differences in adverse events and deaths in paediatric patients randomised to treatment with propofol or standard selective agents for ICU sedation.

Propofol is currently not authorised for sedation in paediatric ICU patients in Ireland and should not be used for this purpose.

Itraconazole (Sporanox)

Itraconazole is a triazole antifungal agent, possessing a broad spectrum of activity. It is active against most of the pathogenic dermatophytes and yeast, but also against several pathogenic moulds and other fungi including *aspergillus* spp, major pathogens in immunocompromised patients.

Recent studies conducted in dogs and healthy human volunteers identified negative inotropic effects with the intravenous formulation of itraconazole. In these studies, once the drug was stopped the negative inotropic effects resolved. A mechanism for these cardiac effects has not been determined.

Since becoming aware of these findings a review of worldwide spontaneous and post-marketing adverse drug reaction (ADR) reports identified cases of congestive heart failure associated with itraconazole use. In some cases the causal relationship was unclear, because of confounding factors, including some cases of serious underlying conditions. However, a number of reports were identified in patients treated with itraconazole for onychomycosis. While the evidence for a clinically significant inotropic effect of oral itraconazole is not as strong, a small negative inotropic effect of itraconazole might cause cardiac decompensation in "at risk" patients.

The product information has been updated to reflect this information and to include additional warnings in the special warnings and special precautions for use, interactions and undesirable effects sections of the documents.

Reference: *Lancet 2001*: **357**: 1766-1767

Clopidogrel (Plavix)

Clopidogrel is a platelet aggregation inhibitor authorised for use in the treatment of atherosclerotic events (MI/stroke due to vascular causes), in patients with a history of symptomatic atherosclerotic disease defined as ischaemic stroke, MI or established peripheral arterial disease. It is estimated that over 5 million patients worldwide have been treated to date.

Reports of serious haemorrhage (occasionally fatal), have been notified with post marketing use of clopidogrel. It is important to note that some of these cases have been associated both with use in licensed indications and in "off label" indications such as coronary artery stenting. This may occur in the presence or absence of thrombocytopenia.

In order to facilitate detection of bleeding disorders and thus reduce the risk of serious bleeding, it is recommended that blood count (red and white cell counts, haemoglobin, haematocrit and platelet count) should be monitored whenever clinical suspicion of bleeding or haematological disorders arise during the course of treatment. Blood count determination should also be performed during the first week of treatment in case of co-administration of clopidogrel with aspirin, NSAIDs, heparin, glycoprotein 11b/111a inhibitors or thrombolytics, which should be undertaken with caution and in patients who may be at risk of bleeding from trauma, surgery or other pathological conditions.

Clopidogrel was first marketed in Ireland in 1998 and to date the IMB has received five reports of bleeding disorders associated with its use.

Prescribers are reminded to report any suspected adverse reactions occurring with this new medicinal product to the IMB in the usual way.

Update on Adverse Drug Reaction (ADR) Reporting

During 2000, the IMB received a total of 1,407 suspected ADR reports occurring in Ireland. This figure represents an increased reporting rate of 39% over the volume of reports received in 1999 and appears to have coincided largely with the initiation of the meningococcal C vaccination programme. The IMB greatly appreciates this increase in reporting and acknowledges the important contribution of busy healthcare professionals to the continued surveillance of the safety of medicines through the voluntary reporting system. While the burdensome nature of form-filling is recognised, the collection of ADR reports is essential to ensure continued, effective surveillance of the safety of licensed medicines.

The following table provides a breakdown of reports by source:

General Practioners	**56.9%**
Pharmaceutical Companies	**20.8%**
Hospital Doctors	**10.4%**
Community Pharmacists	**3.9%**
Hospital Pharmacists	**2.3%**
Nurses	**5.3%**
Dentists	**0.4 %**

All suspected ADRs were reviewed and evaluated prior to inclusion on the IMB's database, with feedback information provided to reporters as appropriate.

The IMB's ADR database includes anonymised case details and is regularly reviewed to identify and evaluate the safety of medicines. This information is used to monitor safety of medicines on an ongoing basis and when considered appropriate, to revise prescribing information accordingly.

The IMB's database currently includes approximately 28,000 adverse reaction reports provided by healthcare professionals and pharmaceutical companies in relation to reports of Irish ADRs, notified since 1968. This information is helpful not only to the IMB in its evaluation of the safety profile of medicinal products, but is also useful for provision of information in response to enquiries from healthcare professionals.

Spontaneous reporting of suspected adverse reactions is an inexpensive and effective method for the lifetime surveillance of medicines following their introduction to the marketplace. While an individual's experience may be limited to one or two cases, when collated with additional reports from other sources, such cases may contribute considerably to the assessment of a possible safety hazard.

Healthcare professionals are reminded that it is not necessary to determine a causal relationship between a drug and subsequent event prior to reporting of suspected adverse drug reactions.

You are particularly reminded to report:

- All suspected adverse reactions to new medicinal products (i.e. those available on the market for less than two years).

- Serious suspected reactions to established medicines. A serious reaction is defined as one which is fatal, life threatening, results in persistent or significant disability/incapacity, results in or prolongs hospitalisation. This definition also includes congenital abnormalities or birth defects and serious adverse clinical consequences.

- Any suspected increase in the frequency of minor reactions.

- Any suspected teratogenic effects.
- Any suspected reactions associated with the use of vaccines.

The IMB is always keen to help, encourage and establish ADR monitoring and reporting practices. Any centres wishing to develop their

reporting system should contact the Pharmacovigilance Unit of the IMB

Product Information

A previous issue of the IMB's Drug Safety Newsletter described the information included in the summary of product characteristics (SPC). As the name suggests, this is a summary of the information, which should allow the prescriber to use the drug in the safest and most appropriate manner. It is the basis of information for doctors on how to use a product safely and effectively. It is also a legal document, in that the content has been agreed between the IMB and the pharmaceutical company and reflects the information provided in support of the product authorisation application.

In keeping with European legislation (EC Directive 92/27), the patient information leaflet (PIL) must reflect all the information contained in the SPC, in lay language. Therefore, details of all contraindications, special warnings and special precautions for use, interactions and undesirable effects must be included in the PIL.

As generic applications are made to the IMB which do not always include all the indications which may apply to the brand leader, SPCs and PILs may not be identical to those of the brand leader. This should be taken into account if/when prescribing generic medications and may need explanation to patients who may be confused by differences in PILs provided. In addition, as some products are authorised through European assessment procedures, there may be some differences in the wording of indications between brand leader and generic products.

Contact Details

Have we got the correct contact details for you?

The IMB is anxious to ensure that our mailing lists for doctors and dentists are accurate. If there are any errors/changes to the address to which this communication was sent, it would be appreciated if you would contact the Pharmacovigilance Unit of the IMB (see below). Details of e-mail addresses are also welcome to facilitate more rapid dissemination of information in the future.